## REMARKS

Claims 24, 25, 28, 29, 32, 33, 36, 37, 40, 41, 43, 44, 47-50, 54, 55 and 57-64 are pending in the present application. Claims 24, 25, 28, 29, 32, 33, 36 and 37 are withdrawn by the Examiner as being directed to different inventions. In light of the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

### I. Recordation of Interview Summary

To record the Interview Summary mailed on May 24, 2011 regarding the above-referenced patent application, applicants concur that the Interview Summary accurately reflects the substance of the telephone interview that took place on May 19, 2011, in which Examiner Amanda Marie Shaw and applicant's representative, Dr. Alice M. Bonnen, participated.

### III. Rejection under 35 U.S.C. § 103.

The Office Action states that claims 40, 41, 43, 44, 47- 50, 54-55 and 57-64 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Beckman et al. in view of Majlessi et al. (*Nucleic Acids Res.* 25:2224-2229 (1998)) and Tourkas et al. (*Nucleic Acids Res.* 30:5168-5174 (2002)). The Office Action states that Beckman et al. teaches that a MB probe can comprise one or more 2'-O-methyl nucleotides (e.g., at its 5' end) or a MB can consist entirely of 2'-O-methyl nucleotides. The Office Action states that Beckman also teaches that the arms of a MB probe that form the stem duplex are about 3-25 nucleotides in length. The Office Action states that Beckman does not teach: (1) a stem comprising one or more unmodified nucleotides, and in the 3' strand of the stem, 2'-O-derviatized nucleotides, wherein each base pair of said stem comprises no more than one 2'-O-derivatized nucleotide and further wherein said probe has better stability and does not open spontaneously in the present of contaminants present in an amplification enzyme mixture; (2) a MB probe wherein at least one base pair of said stem contains no nucleotide or nucleotide analogues having an affinity increasing modification; or (3) a MB probe wherein only one base pair of said stem comprises no nucleotide or nucleotide analogue having an affinity increasing modification. After reciting this lengthy list of what

Beckman does not teach, the Office Action then asserts that the advantages of using of 2'-O-methyl nucleotide probes over 2' deoxynucleotide probes were known as taught by Majlessi et al. and Tourkas et al. On this basis, the Office Action concludes that it would have been obvious to one of skill in the art to have modified the MB probe of Beckman so that the MB probe comprises a stem comprising one or more unmodified nucleotides, and in the 3' strand of the stem, one or more 2'-O-derivatized nucleotides, wherein each base pair of said stem comprises no more than one 2'-O-derivatized nucleotide; wherein at least one base pair of said stem comprises no nucleotide or nucleotide analogue having an affinity increasing modification or wherein only one base pair of said stem comprises no nucleotide or nucleotide analogue having an affinity increasing modification. The Office Action states that although Majlessi et al. and Tourkas et al. compared probes consisting entirely of 2'-O-methyl oligoribonucleotides, one of skill in the art would have recognized that probes consisting of 2'-O-methyl oligoribonucleotides and 2' deoxy oligoribonucleotides would also have some advantageous properties and that determining the optimum placement of the 2'-O-methyl nucleotides in the stem region so that the probe has better stability and does not open spontaneously is considered to be routine experimentation. Specifically, the Office Action states "[i]t is obvious to try different placements of the 2'-O-methyl nucleotides in the stem region, particularly since there are only a limited number of positions in the stem region (Beckman teaches that stems are 3-25 nucleotides long)."

Applicants respectfully disagree. The requirements for a *prima facie* case of obviousness based on "obvious to try" are provided in MPEP §2143(E).

> **E. "Obvious To Try" - Choosing From a Finite Number of Identified, Predictable Solutions, With a Reasonable Expectation of Success**
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> To reject a claim based on this rationale, Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:
>
> (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
>
> (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;

> (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
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> (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
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> The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103."KSR, 550 U.S. at ___, 82 USPQ2d at 1397. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Each of these factual inquiries of MPEP §2143(E) are analyzed below with respect to the presently claimed invention.

(1) A finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem.

The first element required to make a rejection based on the "obvious to try" rationale has not been met because the Office Action has not made a factual finding that there was a recognized problem or need in the art. The Office Action merely states "it would have been obvious to one of skill in the art at the time of the invention to have modified the MB probe of Beckman so that the MB comprised a stem comprising one or more unmodified nucleotides, and in the 3' strand of the stem, one or more 2'-O- derivatized nucleotides, wherein each base pair of said stem comprises no more than one 2'-O- derivatized nucleotide," "[i]t would have been obvious to make a MB probe wherein at least one base pair of said stem contains no nucleotide or nucleotide analogue having an affinity increasing modification," and "[i]t would have been obvious to make a MB probe wherein only one base pair of said stem has contains no nucleotide or nucleotide analogue having an affinity increasing modification." Office Action, pages 5, 8-9, 12, 15, 18 and 21-22. However, the Office Action does not set forth any recognized problem or need that might be solved by combining these references in the proposed manner to produce the claimed invention.

The present invention overcomes a specific problem identified by applicants, as set forth in the specification, which was the development of MBs that have lowered spontaneous (unwanted) opening of the probe in the presence of contaminants present in an amplification enzyme mixture comprising said molecular beacon probe compared to a molecular beacon probe without said stem. It was observed that different batches of the same enzymes (e.g., T7), even from the same supplier, with the same specific activity and volume activity, had different levels of unwanted opening (resulting in false positive readings) of the MBs when the MBs consisted of natural deoxyribonucleotides. The present applicants unexpectedly found that this phenomenon was more effectively addressed by introducing fewer 2'-O- methyl groups in the MB instead of substituting all the natural deoxyribonucleotides with 2'-O- methyl groups (*See,* Specification, for example, page 3, lines10-17 and lines 28-32; page 5, lines 18-25).

The problem(s) to be solved as set forth in Beckman et al. and Tsourkas et al. is limiting nuclease degradation of the MBs, thus reducing fluorescent signals unrelated to probe/target hybridization (Tsourkas et al., abstract, page 5168, col. 2, para. 20; Beckman et al., abstract, para. 37-39, 42, 43 and 74) and the problem to be solved in Majlessi et al. is to identify MBs with better binding to their target nucleic acids, specifically to target RNA molecules (Majlessi et al., abstract, page 2224, col. 2, second para). Thus, it is clear that the applicants recognized, independent of the teachings of the cited references or other information upon which this rejection is based, the need for a MB having lower spontaneous opening of the probe in the presence of contaminants present in an amplification enzyme mixture comprising the MB probe as compared to a molecular beacon probe without said stem and the solution to this problem is the partial replacement of the natural deoxyribonucleotides with 2'-O- methyl groups. As set forth above, none of the cited references identify or resolve this problem and therefore fail to identify the need for a MB probe of the present invention, which allows for the detection of a target nucleic acid using a MB probe, wherein the spontaneous opening of the probe in the presence of contaminants present in an amplification enzyme mixture comprising the MB probe is lowered as compared to a molecular beacon probe without said stem.

(2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem.

Likewise, the second element of the "obvious to try" rationale has not been met because the Office Action has not made the factual finding that there are a "finite number of identified, predictable potential solutions to the art recognized need or problem." Even assuming *arguendo* that the problem to be solved as taught by the present invention had been known in the art, one of ordinary skill in the art would have had to conclude that the number of identifiable, predictable potential solutions to this problem would not be finite. Instead, one would have had to choose from an extremely large number of possible solutions in order to identify any particular MB that would solve the problem described by the claimed invention.

As pointed out in the Office Action, Beckman et al. teaches that a MB stem can be 3 to 25 nucleotides in length; thus length of the MB is a choice that must be made (Beckman, para. 0097). Further, there would be four choices for every base pair: (1) modified-modified, (2) modified-unmodified, (3) unmodified-modified and (4) unmodified-unmodified. Thus, for a MB having only 3 base pairs in the stem, there are 64 options from which to choose. Further, this large number of options does not even take into consideration the choice of nucleotide (A, T, C, or G) for each base of a base pair. For a MB stem having 4 base pairs, the choices are among 256 different arrangements. Similarly, for 5 base pairs there are 1024 options; for 6 base pairs there are 4096 options; for 7 base pairs there are 16,384 options; for 8 base pairs there are 65,536 options; and for 9 base pairs there are over 260,000 options. Jumping to a MB having a stem comprising 9 base pairs to one comprising 25 base pairs as taught in Beckman et al., there are over $1.1\times10^{15}$ potential solutions to the problem with no guidance from the cited references as to which to select or how to even narrow the options. At best Beckman suggests a 2'-O-derivatized nucleotide at the 5' end of the MB or a MB composed entirely of 2'-O-methyl oligoribonucleotides or entirely of 2' deoxy oligoribonucleotides. Tsourkas et al. and Majlessi et al. teach only MBs composed entirely of 2'-O-methyl oligoribonucleotides or 2' deoxy oligoribonucleotides. It is apparent that none of the molecular beacons of the presently claimed invention could be considered to be included among a "finite number of identifiable predictable, potential solutions" as set forth in the Examination Guidelines. *See, Takeda Chemical Indus. v. Alphapharm Pty., Ltd.* (492 F.3d 1350 (Fed. Cir. 2007)), which states:

> In *Pfizer*, we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. Noting that our conclusion was based on the "particularized facts of the case," we found that the prior art provided "ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate."

*Id.* at 1359-60 (citation removed). Thus, the court in *Takeda* confirmed the holding in *Pfizer* that a long list of possible choices as provided in the prior art. is insufficient for a finding of obviousness in the absence of further teachings that narrow the choice down to a small number.

(3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success.

The third element needed to make a rejection based on the "obvious to try" rationale has also not been met because the Office Action fails to demonstrate that one of ordinary skill in the art could have pursued any potential solutions with a reasonable expectation of success. As discussed above, even assuming *arguendo* that the problem to be solved as defined by the present invention was known and then further assuming that the solution was to incorporate modified nucleotides into a MB, the number of potential solutions clearly would not be finite but instead would be quite large. The cited art provides no guidance for selecting among this very large number of potential solutions which may solve the problem of spontaneous opening of the MB, not predictability that any of the potential solutions would provide the desired effect (lowered spontaneous opening) and therefore, none provide any reasonable expectation of success in constructing a MB probe as claimed by the present invention.

Contrary to the teachings of the cited references, applicants have unexpectedly discovered that the designing of a MB probe having better stability and which does not open spontaneously depends both on the presence and position of the nucleotide analogues in the stem and whether the nucleotide analogues are base-paired with other nucleotide analogues or with

unmodified nucleotides. See, for example, Table 6 of Example 4 of the present specification, which shows that the use of MB probes consisting entirely of base pairs having only one type of nucleotide (2' deoxy nucleotides (unmodified) or 2'-O-methyl nucleotides (modified)) results in higher levels of spontaneous opening of the probe. Notably, the MB4 probe having all modified nucleotides has a 22% higher spontaneous opening (IBL-Increase of Baseline) than Reference MB, which is comprised entirely of unmodified nucleotides. The MB4 probe also has a higher spontaneous opening as compared to most MB probes comprising a combination of unmodified and modified nucleotides (44-94%). MB probes having 2'-O-methyl nucleotides base-paired with unmodified nucleotides also show increased stability, which is surprising in view of what was known in the art at the time the present invention was made. *See* Tsourkas et al., page 5173, first column, last sentence (teaching that the greater stability of the stem-loop structure of the MB probes is the result of the 2'-O-methyl/2'-O-methyl interactions). Furthermore, as demonstrated with probes MB8 and MB9 (Figures 17 and 18, respectively), having one base pair in the stem of the MB that is comprised of unmodified nucleotides, results in an unexpectedly low level of spontaneous opening as compared with probes not having such structure (see, Example 4, Table 6, and Figures 17 and 18; MB8 has 63% and 70% less spontaneous opening than MB6 and MB7)). Such a result could not have been predicted based on the teachings or suggestions of the cited references or based on what was commonly known at the time the present application was filed.

The Office Action asserts that determining the optimum placement of the 2'-O-methyl nucleotides in the stem region would be routine experimentation and it would have been obvious to try different placements because there are only a limited number of positions within the stem region. However, as discussed above, there are an extremely large number of positions and alternative placements both among and between base pairs in a MB stem (even in an MB stem consisting of only three base pairs). To determine the optimum placement of 2'-O-methyl nucleotides in the stem region would require the generation and testing of an extremely large population of MBs in order to discover which MB solved the problem of unwanted opening of the MB. As discussed in the publication entitled "Molecular beacon sequence design algorithm" by W.T. Monroe and F.R. Haselton (BioTechniques 34:69-73 (2003)) this approach would be

considered unpractical by one of ordinary skill in the art. Specifically, Monroe and Haselton state "[t]he stem region sequence can contain any possible combination of nucleotides.... While one could in theory synthesize a large number of molecular beacons with different stem sequences and then test each one for effectiveness, the current costs associated with synthesizing the oligonucleotide with attached quencher and fluorophore makes this unpractical" (*see,* abstract, page 69, last full paragraph through page 70, first paragraph). Monroe and Haselton report that the cost of generating a single MB is about $400 (page 70, first paragraph).

Thus, none of the cited art teaches or suggests that the content and placement of the modified nucleotides in a MB probe with respect to unmodified nucleotides would play a role in the functional features of a MB probe and randomly generating and testing of MBs would not be practical as the number of possibilities is extremely large and the cost is considerable. Accordingly, due to their lack of teachings, none of the cited references provide one of ordinary skill in the art with any reasonable expectation of success in achieving the presently claimed invention.

(4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The Office Action has not articulated any other findings that may explain the conclusion of obviousness.

As stated in the USPTO guidelines and discussed above, if any of the factual findings required for making a rejection based on the obvious to try rationale cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. Because none of the factual findings required for an obviousness rejection based on the "obvious to try" rationale have been made with respect to claims 40, 41, 43, 44, 47- 50, 54-55 and 57-64 of the present invention, applicants submit that the Office has not established a *prima facie* case of obviousness. Therefore, applicants respectfully submit that claims 40, 41, 43, 44, 47- 50, 54-55 and 57-64 are allowable in view of the cited references and request that the rejection of these claims be withdrawn.

Accordingly, Applicants submit that the present application is in condition for allowance and the same is earnestly solicited. Should there be any remaining concerns the Examiner is encouraged to contact the undersigned attorney by telephone.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of $130.00 as fee for a one-month extension of time for large entity. This amount is believed to be correct. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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